

## REMARKS

Claims 1, 13, 17, and 19-24 are pending. Claims 1, 13, 17, and 19-24 are rejected under 35 U.S.C. § 112, first paragraph. Applicants address each rejection as follows.

### Claim Amendments

Claims 1, 17, 21, and 22 have been amended to recite “nucleic acid sequences” encoding particular polypeptides. Support for these amendments is found, for example, at page 26, line 20, to page 27, line 1, page 52, lines 20-22, and page 78, line 21, to page 79, line 2, of the specification as filed. In view of the amendments to claims 1 and 17, the language of dependent claims 13, 19, and 20 has also been amended. No new matter has been added by the present amendments.

### Rejection under 35 U.S.C. § 112, first paragraph

Claims 1, 13, 17, and 19-24 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that is not described in a specification in such a way as to reasonably convey to one skilled in the art that Applicants, at the time the application was filed, were in possession of the claimed invention. Claims 1, 13, 17, and 19-24 are also rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Applicants submit that these bases for rejection should be withdrawn.

### *Written Description*

In rejecting claims 1, 13, 17, and 19-24 for an asserted lack of written description in the specification, the Office states (page 3):

[T]he specification fails to disclose what represent human FKHR and AFX gene [sic] especially in view of the fact that the scope of gene encompasses not only the ORF but also regulatory regions and the genomic sequence etc.

\* \* \*

[B]esides the human FKHR and AFX encoding sequences the specification fails to disclose any other gene that comprises any variant of SEQ ID NO:57 and SEQ:102, wherein the gene is obtained from [sic] any other organism and is capable of functioning like an insulin signals [sic] and convergence with DAF-7-like Smad signals.

With respect to the first basis for the rejection, as noted above, independent claims 1, 17, 21, and 22 have been amended to delete the term “gene” and, instead, recite “nucleic acid sequence encoding” a particular polypeptide. This amendment overcomes the Office’s concern regarding the use of the term “gene” for all of claims 1, 13, 17, and 19-24, and this basis for the rejection may be withdrawn.

### Claims 21 and 22

With respect to the second basis for the rejection as directed to claims 21 and 22, there can be no question that the written description requirement is satisfied. These claims do not cover “any variant of SEQ ID NO:57 and SEQ:102,” but rather are directed to nucleic acid sequences encoding “human FKHR” and “human AFX,” respectively. These coding sequences were known in the art at the time the application was filed. In this regard, Applicants direct the Office’s attention to the February 25, 2005 reply in

which Applicants cite GenBank Accession Number U02310, UniProt Entry P98177, and the abstract of Borkhardt et al. (Oncogene 14:195-202, 1997) in support of the public availability of the human FKHR and AFX open reading frames as of the date of filing. Given that claims 21 and 22 recite nucleic acid sequences encoding polypeptides having sequences that were known at the time of filing, one skilled in the art would clearly recognize which sequences are encompassed by the claims, and on this basis alone, Applicants submit that claims 21 and 22 find adequate written description in the specification.

Moreover, on this point, Applicants also direct the Office's attention to a recent decision by the United States Court of Appeals for the Federal Circuit, *Capon v. Eshhar*, 418 F.3d 1349, 76 U.S.P.Q. (BNA) 1078 (Fed. Cir. 2005). The *Capon* decision is based on an interference proceeding involving claims directed to chimeric genes for the production of membrane-bound proteins. The Board of Patent Appeals and Interferences ("the Board") rejected the claims of both parties under 35 U.S.C. § 112, first paragraph, noting that the claims lacked an adequate written description in the specification. The Board concluded that the written description requirement necessitated a listing of the specific nucleotide sequences of the claimed DNA. On appeal, the Federal Circuit reversed, with the court stating:

The chimeric genes here at issue are prepared from known DNA sequences of known function. The Board's requirement that these sequences must be analyzed and reported in the specification does not add descriptive substance. The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the

structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes. (Emphasis added.)

*Capon*, 418 F.3d at 1358.

The Federal Circuit also stated that “the Board erred in ruling that § 112 imposes a *per se* rule requiring recitation in the specification of the nucleotide sequence of claimed DNA, when that sequence is already known in the field.” *Capon*, 418 F.3d at 1360. As such, the written description requirement must be applied in the context of the particular invention and the state of the knowledge in the art.

The presently claimed invention is based on the finding that DAF-16 is an appropriate target molecule for identifying candidate modulatory compounds for impaired glucose tolerance conditions. The connection between DAF-16 and an insulin signaling-like pathway was discovered by Applicants and is now well established in the art. A role in insulin sensitivity for both FKHR and AFX has also been recognized in the art. Following the principles set forth in the *Capon* decision, the nucleic acid sequences encoding FKHR and AFX need not be reiterated, described, or reproduced in the instant specification to comply with the written description requirement of 35 U.S.C. § 112, first paragraph. The written description rejection of claims 21 and 22 should be withdrawn.

#### Claims 1 and 17

Applicants submit that their specification also provides a written description of the invention of claims 1 and 17 in sufficient detail to satisfy the standard set forth by the Patent Office in its Written Description Guidelines and by the Federal Circuit in *Lilly*. In

particular, *Lilly* specifically states that the written description of a genus of DNA may be achieved by a “recitation of structural features common to members of the genus.”

*Regents of University of California v. Eli Lilly & Co.*, 119 F.3d 1159, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997). Moreover, the Guidelines for Examination of Patent Applications Under 35 U.S.C. 112 ¶1, “Written Description” Requirement, 66 Fed. Reg. 1099 (Jan. 5, 2001) similarly state:

The written description requirement for a claimed genus may be satisfied ... by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

Applicants, in the February 25, 2005 reply, laid out detailed arguments in support of the specification falling within the written description standard set forth in *Lilly* and in the Written Description Guidelines. In the present action the Office’s written description rejection appears to turn on the assertion that 5% variation affects folding and function of a protein. In particular, the Office states (pages 5-6):

The scope of claim 1 also encompasses any gene containing variation in the conserved motif (SEQ ID NO:54), which is considered germane to the functional activity of daf-16 polypeptide. For example 5% variation (95% identical) in the conserved domain of a gene or a hybridization product as claimed would certainly affect proper folding and biological activity if amino acids that are critical for such functions are substituted, since the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable ... According to these facts, one skill[ed] in the art would conclude that applicant was not in possession of the claimed genus. (Emphasis added, in part.)

Applicants respectfully disagree.

The Office appears to imply that many sequences falling within the claims would not be functional. However, the Office has provided no evidence in support of this assertion, whereas Applicants, for example, in the February 25, 2005 reply, provided evidence indicating that sequences sharing far less than 95% identity could functionally substitute for each other. In particular, as noted in Applicants' February 25, 2005 reply, the specification teaches, for example, at page 55, lines 22-27, that FKHR and AFX are excellent candidates for serving the same function as *C. elegans* DAF-16. Applicants also note, in reference to the Ruvkun Declaration submitted with the July 24, 2003 reply, that inventor Dr. Gary Ruvkun has demonstrated that FKHL1 can functionally substitute for *daf-16 in vivo*. Thus, as is taught in Applicants' specification, FKHR can serve the same function as DAF-16.

This experimental result directly contradicts the Office's position as FKHR is only approximately 71% identical to the sequence of SEQ ID NO:54, as shown by the alignment in Figure 21A. Consequently, Applicants have demonstrated that a sequence that is *less* homologous than required by the present claims can functionally substitute for DAF-16 in insulin signaling. Applicants submit that the degree of sequence identity required by claim 1, 95%, is a recitation of a structural feature common to members of the genus. Claim 1 also satisfies the written description requirement by requiring the polypeptide encoded by the nucleic acid sequence to function in insulin signaling.

Similarly, with regard to claim 17, and its dependent claims, Applicants submit that these claims also clearly satisfy the written description requirement. On this issue, in the February 25, 2005 reply, Applicants directed the Office's attention to Example 9: Hybridization of the U.S. Patent & Trademark Office's Written Description Guidelines (<http://www.uspto.gov/web/menu/written.pdf>; "the Guidelines"). Applicants noted that the facts of the present case are squarely within these Guidelines and that the highly stringent hybridization requirement in claim 17 limits the claim to structurally similar nucleic acids which, when combined with the functionality requirement, describes a genus of nucleic acid molecules that is well within the written description requirement. These assertions are not disputed by the Office in the present action. Consequently, like the requirement for at least 95% identity in claim 1, the highly stringent hybridization requirement of claim 17 also limits the claim to sequences that, in view of the specification and Dr. Ruvkun's Declaration, would be expected to function in insulin signaling.

Applicants further note that the experiments described in Dr. Ruvkun's Declaration using FKHR and DAF-16 are consistent with results obtained by others with nucleic acid sequences homologous to *C. elegans* nucleic acid sequences. For instance, as described by Haun et al. (Proc. Natl. Acad. Sci. USA 95:5072-5075, 1998; "Haun;" copy enclosed as Exhibit 1), zebrafish *nkx2.5* and *C. elegans ceh-22* are functionally

interchangeable in *C. elegans* (page 5074, left column).

Haun notes that the “[a]mino acid sequence identity between Nkx2.5 and CEH-22 is greatest within the homeodomain (68% identity), although two short regions of similarity are also found in conserved regions upstream and downstream of the homeodomain” (page 5074, top of right column). Alignments of the CEH-22 and Nkx2.5 sequences are shown in Figure 3 of Haun. Here, sequences that share only 68% identity (32% variation) in the most conserved region can still functionally substitute for each other in *C. elegans*. Again, this experimental result is contrary to the Office’s assertion that 5% variation in a conserved region would “certainly affect proper folding and biological activity if amino acids that are critical for such functions are substituted,” Haun demonstrates that, despite 32% variation in the most conserved region, CEH-22 and Nkx2.5 can still functionally substitute for each other. Haun therefore supports Applicants’ contention that sequence identity of 95% to a given sequence and hybridization under highly stringent conditions are reasonable criteria for defining the structural features common to Applicants’ genus of workable nucleic acid sequences.

On this point, Applicants also direct the Office’s attention to Levitan et al. (Proc. Natl. Acad. Sci. USA 93:14940-14944, 1996; “Levitan,” copy enclosed as Exhibit 2). As stated in the abstract of Levitan, normal human presenilins can substitute for *C. elegans* SEL-12 protein in functional assays *in vivo*. The *C. elegans* SEL-12 protein is about 50% identical at the amino acid sequence level to human presenilins PS1 and PS2 (see, e.g.,



page 14940, top of right column). Accordingly, like Haun, Levitan describes proteins that are far less than 95% identical to a *C. elegans* protein, yet are still able to functionally substitute *in vivo* for the *C. elegans* polypeptide.

The above evidence demonstrates that Applicants' specification satisfies the written description requirement for claims 1 and 17. Applicants demonstrate that sequences that are far less than 95% identical can functionally substitute for each other *in vivo*. As such, at least 95% identity or hybridization under highly stringent conditions are reasonable criteria for defining structural features common to nucleic acid sequences encompassed by claims 1 and 17. Further, claims 21 and 22 recite nucleic acid sequences encoding polypeptides having sequences publicly known at the time of filing. One skilled in the art would recognize which sequences are encompassed by claims 21 and 22. As such, Applicants submit that the specification provides adequate written description for the nucleic acid sequences recited in the present claims. The written description rejection of claims 1, 13, 17, and 19-24 should be withdrawn.

#### *Enablement*

Claims 1, 13, 17, and 19-24 are also rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. In particular, the Office asserts (pages 7-8):

The specification as filed fails to identify the relevant characteristics of the gene (as claimed) that a person skilled in the art would recognize the human FKHR and human AFX genes. For example, the specification fails to disclose the nucleotide sequence, which comprises a gene encoding human FKHR and AFX genes.

\* \* \*

Since the specification fails to disclose what represent[s] a gene that encodes a polypeptide having 95% identity to SEQ ID NO:54, a gene that hybridizes to nucleotides of SEQ ID NO:57 or SEQ ID NO:102, and human FKHR and AFX gene, it is unclear how one skilled in the art would use the invention as claimed without further undue amount of experimentation, especially in view of the fact that identification of a gene encompasses not only the ORF but also regulatory regions and the genomic sequence etc.

Applicants submit that the claims, as amended, are free of this basis for rejection.

The Office's rejection appears to be based, in part, on the interpretation that the term "gene" encompasses not only the coding sequence of a nucleic acid sequence, but also regulatory regions and the genomic sequence. The claims have been amended to no longer recite the term "gene." Instead, the claims, as amended, recite "a nucleic acid sequence encoding" a particular polypeptide. This basis for rejection may be withdrawn.

With regard to the Office's further rejection concerning the amount of experimentation required to practice the claimed invention, Applicants note that the test of enablement is "whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with the information known in the art without undue experimentation." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d. 1318 (Fed. Cir. 1985). The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. As detailed below, Applicants submit that it would not require undue experimentation to make and use the

invention within the full scope of the present claims.

#### Claims 21 and 22

Claims 21 and 22 are directed to methods that make use of nucleic acid sequences encoding a human FKHR polypeptide and a human AFX polypeptide, respectively. As noted in Applicants' February 25, 2005 reply, and as reiterated above, the nucleic acid sequences encoding human FKHR and AFX polypeptides, as well as the polypeptide sequences themselves, were known in the art at the time the application was filed. No experimentation is therefore required to practice the methods of claims 21 or 22, or their dependent claims. The rejection, as applied to these claims should be withdrawn.

#### Claims 1 and 17

Claims 1 and 17 recite methods that make use of nucleic acid sequences encoding a mammalian polypeptide having at least 95% identity to SEQ ID NO:54 and that functions in insulin signaling (claim 1), and nucleic acid sequences hybridizing under highly stringent conditions to the complement of a nucleic acid sequence encoding the sequence of SEQ ID NO:57 or SEQ ID NO:102 and that functions in insulin signaling (claim 17). Applicants submit that claims 1 and 17, and their dependent claims, are also enabled by the specification as filed.

The amount of experimentation required to identify other nucleic acid sequences encoding the polypeptides recited in claims 1 and 17 is routine in the art of molecular biology and, therefore, does not constitute undue experimentation. In particular,

identifying sequences that fall within the scope of claim 1 or 17, i.e., sequences that encode a polypeptide having at least 95% identity to the sequence of SEQ ID NO:54 or that hybridize under highly stringent conditions to the complement of the sequence of SEQ ID NO:57 or 102 requires nothing more than standard methods and routine experimentation. Moreover, identifying whether such sequences encode a polypeptide that functions in insulin signaling is also standard in the art. Exemplary assays that may be used to determine whether a polypeptide functions in insulin signaling include the mammalian cell culture and *C. elegans* assays described in the specification, for example, at page 20, lines 9-12, page 80, lines 1-16, and page 90, line 12, to page 91, line 15.

Applicants also note that the Ruvkun Declaration submitted with Applicants' July 24, 2003 reply establishes that human FKHR can functionally substitute for DAF-16 in *C. elegans*. Thus, Applicants have established that a related human polypeptide (which, in fact, is less than 95% identical) can function to provide insulin-signaling activity that is similar to *C. elegans* DAF-16. In fact, Dr. Ruvkun noted that "[o]ther highly similar DAF-16 family members would also be expected to substitute for *C. elegans* DAF-16."

Furthermore, the results described by Dr. Ruvkun for human FKHR and *C. elegans* DAF-16, mirror those obtained with other polypeptides that are homologous to *C. elegans* polypeptides. As noted above, Haun and Levitan describe functional substitution of zebrafish and human polypeptides for *C. elegans* polypeptides, where the polypeptides are far less than 95% identical. Indeed, the polypeptide described by Haun is, *in its most*

*conserved domain*, only 68% identical to the related *C. elegans* polypeptide, yet this polypeptide can functionally substitute *in vivo* for the *C. elegans* polypeptide.

In view of the above evidence, the Office's concern that the claimed sequences encompass variation in "the conserved motif (SEQ ID NO:54) or a hybridization product that binds SEQ ID NO:57 or SEQ ID NO:102, which is considered germane to the functional activity of [a] daf-16 polypeptide" is overcome. The enablement rejection of claims 1, 13, 17, and 19-24 should be withdrawn.

## CONCLUSION

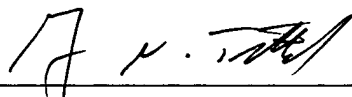
Applicants submit that the application is now in condition for allowance, and this action is hereby respectfully requested.

Enclosed is a Petition to extend the period for replying to the Office Action for three (3) months, to and including January 23, 2006, as January 22, 2006 was a Sunday. Also enclosed is a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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